Message

From: Walsh, Patrick [patrick-walsh@denka-pe.com]
Sent: 7/8/2020 10:49:29 PM
To: Vandenberg, John [Vandenberg.John@epa.gov]
CC: Orme-Zavaleta, Jennifer [Orme-Zavaleta.Jennifer@epa.gov]; Cascio, Wayne [Cascio.Wayne@epa.gov]; Dunlap, David [dunlap.david@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]
Subject: Ramboll's final comments on EPA Peer Review Materials
Attachments: ATT00001.txt; Background for Peer Review of Chloroprene PBPK Modeling_full comments_07072020.docx; Background for Peer Review of Chloroprene PBPK Modeling_Ramboll new comments_07072020.docx; Draft_Charge_questions_for_Peer_Review_of_Chloroprene_PBPK_Modeling_changes_full comments_07072020.docx; Draft_Charge_questions_for_Peer_Review_of_Chloroprene_PBPK_Modeling_changes_Ramboll new comments_07072020.docx; Chloroprene_uncertainty_analyses_formatted_EPA.05-20-2020 full comments_07072020.docx

Importance: High

John,

Hope you had a restful weekend and holiday!

Before I forget, I still haven't seen the FRN yet. Do you have any idea when it will be published?

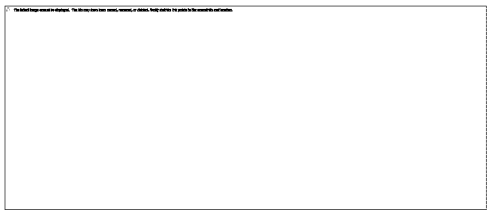
As for the documentation, I'm including Ramboll's comments on the background, charge, and uncertainty analysis documents. Notice that, for convenience, we broke out the few new comments into a cleaner document so they'll be easier to follow. The idea is that we think most of our remaining concerns can be settled during the peer review process, and we would like to get there sooner rather than later, given the fact that we first looked at peer review documents from EPA more than 9 months ago.

To that end, we appreciate EPA's consideration of our comments to date on the materials for the peer review of the Ramboll (2020) model. We have a few remaining comments for EPA to consider as part of the peer review materials; however, we don't want any further delays in initiating the peer review process. We ask that finalizing these materials be a priority so that the Ramboll (2020) model can move into peer review as soon as possible. Our remaining comments are limited to:

- In the Background Document:
  - We had added some language to clarify the introduction of a new dose metric (tissue concentration of the parent chemical) that is not part of the Ramboll (2020) report and is under consideration by EPA. While we have not modified the text, we do provide comments for consideration related to the science surrounding the proposed use of tissue concentration as a dose metric for the cancer risk assessment, i.e., that the science does not support using tissue concentration as a dose metric because it is inconsistent with the accepted mode of action.
- In the Charge Questions Document:
  - We appreciate the input on the tiered process and agree with most of the suggested edits. However, there is still confusion over the use of the Wood et al. (2017) paper as a way to evaluate the ability of IVIVE to be used for chloroprene. We have suggested additional edits to clearly point out that the Wood et al. (2017) paper focuses on oral dosing of drugs, not inhalation of volatile compounds, such as chloroprene. It is probably most appropriate to remove reference to the Wood paper entirely as a result.
- In the Uncertainty Analysis Document:
  - We recognize that EPA is not requesting comments on this document; however, we think it is important to convey anything we have identified that could be an incorrect assumption and impact the results of the analysis. In particular, we have noted some aspects of the MCMC approach that we believe are less than optimal and could result in failure to obtain convergence for the parameter estimates. We would be happy to continue the dialog with the EPA scientists performing the analysis to optimize the likelihood of success.

o We also have significant concerns surrounding this new, complex uncertainty analysis of the human lung tissue metabolism data in order to estimate an alternative value. Because these data are highly uncertain, any resulting estimates from this complex analysis would not provide a reliable alternative to the estimates obtained using currently accepted approaches.

Again, we appreciate the opportunity to work with EPA to finalize these materials for the peer review. Please let us know at your earliest convenience whether there are any remaining questions or if these materials are ready to be finalized.



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